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| 10/679,699 | 10/02/2003 | David Bar-Or | 4172-85 | 2007 |

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| EXAMINER | |
|---|---|
| EMCH, GREGORY S | |
| ART UNIT | PAPER NUMBER |
| 1649 | |

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| 06/04/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/679,699 | BAR-OR ET AL. | |
| | Examiner | Art Unit | |
| | Gregory S. Emch | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *47-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Amendment*

Claims 1-46 have been canceled and new claims 47-54 have been added as requested in the amendment filed on 07 March 2007. Following the amendment, claims 47-54 are pending in the instant application.

Claims 47-54 are under examination in the instant office action.

The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicants' response and withdrawn.

### *Information Disclosure Statements*

A signed and initialed copy of the IDS paper filed 01 February 2007 is enclosed in this action.

### *Claim Rejections - 35 USC § 112, first paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter, which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

In the reply filed on 07 March 2007, Applicants assert, "New Claim 47 corresponds to canceled Claim 17, which is included in the above rejections. However, Applicants have clearly provided an enabling description of the claimed method of diagnosing and monitoring multiple sclerosis and clearly had possession of the claimed invention at the time of the filing of the application. See, e.g., the following portions of the application: page 7, lines 3-13; page 19, line 16 through page 20, line 11; and Example 2. Accordingly, Applicants submit that new Claims 47-54 are adequately supported by the specification and comply with the requirements of 35 U.S.C. § 112, first paragraph, and request that the rejection based on these requirements be withdrawn."

Applicants' arguments have been fully considered and are only partially persuasive. Note that the written description rejection under 35 U.S.C. 112, first paragraph has not been applied to the newly presented claims.

However, with regards to enablement of the currently pending claims, as referred to previously, Applicants' data in the specification was obtained from patients pre-selected for having multiple sclerosis (active or non-active). Further, Applicants' data are correlative only; no data is presented regarding diagnosis resulting directly from the claimed methods, i.e., wherein the initial diagnosis is not known. Thus, there is no true nexus established between Applicants' data and diagnosis or monitoring of MS.

Accordingly, the art teaches that diagnosis of MS is unpredictable. For example, Bielekova et al. (cited in previous office action) teaches, "multiple sclerosis is a complex disease, as several pathophysiological processes (including inflammation, demyelination, axonal damage and repair mechanisms) participate in the disease process. Furthermore, as new pathological evidence reveals, these processes are not uniformly represented across patient populations but can selectively predominate in individual patients, thus contributing to the heterogeneity in phenotypic expression of the disease, its prognosis and response to therapies" (Abstract). Bielekova et al. defines the term biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention" and defines a surrogate endpoint as "a biomarker that is intended to serve as a substitute for a clinically meaningful endpoint and is expected to predict the effect of a therapeutic intervention" (pp.1463-4). Further, the reference teaches that there are two conditions that ensure the surrogacy of a biomarker: 1) a strong and significant correlation between the biomarker and a clinical endpoint and 2) the biomarker must fully capture the net effect

of the treatment on the true clinical endpoint. The reference also teaches that "this is virtually impossible, because some of the adverse effects of therapy may be completely unrelated to the pathophysiology of the disease and yet may negatively influence the clinical endpoint...In multiple sclerosis, the situation is further complicated by the fact that the disease pathophysiology is complex and the applied therapy may positively influence only one of the contributing processes (e.g. effect of immunosuppressive therapies on inflammation) and have no effect, or potentially have even negative influence on others" (p.1464). Thus, even with further clinical measures, given the art-accepted unpredictable nature of diagnosing or detecting MS, one could not be reasonably assured that the claimed invention would be indicative of said disease.

Further, although the Examiner assumes that measuring CNS markers would be preferred in the claimed methods, DKPs are not only expressed in the brain. For example, Jara et al. (non-patent literature citation no. 6 on IDS dated 01 February 2007) teach that DKPs are distributed in a variety of body fluids, including plasma, serum, cerebrospinal fluid, and urine and in a variety of tissues, including brain, gut and skin (p.259, col.2). The Jara et al. reference also teaches elevated levels of DKPs in patients with systemic lupus erythematosus (entire document). Therefore, again, the art indicates the invention will be unpredictable with respect to diagnosing MS, since altered levels of the claimed biomarker could indicate a different pathological condition, such as lupus.

Furthermore, the prior art discussed above does not address bodily fluid samples other than plasma, CSF, serum or urine. Given the state of the prior art and given the

lack of guidance presented in the specification, it is unclear how the artisan would detect the claimed biomarkers from saliva, for example, and would then correlate such detection to the status of MS in a patient. Such enabling details are missing from Applicants' disclosure and thus, the skilled artisan would have to perform undue trial and error experimentation to practice the claimed invention.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Due to the large quantity of experimentation necessary to establish a nexus between the claimed assay methods reciting truncated disease associated proteins and the diagnosis and/or monitoring of MS, given the lack of direction/guidance presented in the specification, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the claimed methods, and the breadth of the claims which encompass methods of diagnosing or monitoring MS in any bodily fluid or tissue sample, undue experimentation would be required of the skilled artisan to practice the claimed invention.

## *Conclusion*

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is 571-272-8149. The examiner can normally be reached Monday through Friday from 9:00AM to 5:30PM (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gregory S. Emch, Ph.D.
Patent Examiner
Art Unit 1649
15 May 2007

ELIZABETH C. KEMMERER. PH.D.
PRIMARY EXAMINER